

# Multiple Approaches to Myeloma

*A native of Sweden, Ola Landgren, M.D., Ph.D., trained as a hematologist at the Karolinska Institute in Stockholm, where he also took advantage of the strong medical database resources in Scandinavia to study cancer at a population level. Initially intending to spend only two years at NCI, Landgren opted to remain as an Investigator in the Medical Oncology Branch of CCR because of the unique opportunities to take his observational findings back into the clinic and address his longstanding interest in multiple myeloma. His recent finding that multiple myeloma is consistently preceded by an asymptomatic precursor state—known by the acronym MGUS—has opened a unique window of opportunity for studying the progression of this fatal disease.*

Multiple myeloma is a cancer that affects plasma cells in the bone marrow. These cells normally play a critical role in adaptive immunity by producing the antibodies that target infection and disease. In multiple myeloma, genetically aberrant plasma cells proliferate and produce excess antibody or antibody fragments, which show up clinically as M proteins (monoclonal gamma-globulins) in blood and sometimes urine.

In otherwise healthy individuals, normal plasma cells constitute less than five percent of the cells in healthy bone marrow. However, in multiple myeloma patients, abnormal plasma cells typically account for 10 percent or more of all cells. These cells can also circulate in the bloodstream and accumulate in bone marrow at sites far removed from the original source of the aberrant cells. This abnormal accumulation eventually results in damage to the bones and surrounding tissue, and the term

“multiple myeloma” comes from the scattered bone lesions that are observed in later stages of the disease. Resulting damage eventually includes kidney failure, recurrent infections, abnormally high calcium levels in the blood, and anemia. At this time, it remains incurable.

## Catching it Early

In cancer, early diagnosis is quite often the difference between life and death. Catching cancer before it starts, of course, is the best possible situation. However, in most cases, by the time patients come to our attention clinically, the cancer is well rooted in the body.

In the case of multiple myeloma, we know that there is a related condition called monoclonal gammopathy of unknown significance (MGUS). The name comes from the M proteins that are found in the serum in the absence of any disease pathology. In fact, MGUS is present in approximately three percent

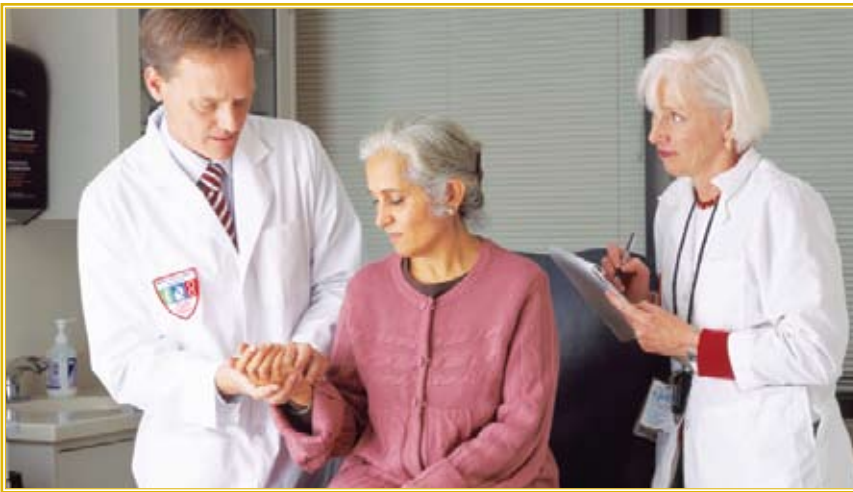
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of the general population above the age of 50. There are no symptoms associated with MGUS—it is usually diagnosed when abnormal M-protein levels turn up during diagnostic tests performed for other reasons (see “The Doctor-Patient Relationship,” page 32). We also know that for people with MGUS, the risk of developing multiple myeloma is significantly increased relative to the general population.

From the time I was working in Sweden, I have been fascinated by the existence of this precursor disease with a high risk of transformation. Using the unique population-based medical history databases that exist as part of universal health care in Scandinavia, we were able to identify over 4,000 MGUS patients and over 14,000 first-degree relatives of these patients. Equally important, we were also able to identify individuals and their relatives that were well matched to our patient population in important characteristics to serve as controls. In that study, which we published last year in the journal *Blood*, we found that MGUS is about three times as common in families as compared to controls, which indicated to us that susceptibility genes and/or shared environmental influences are involved in the disorder. We have since shown that the risk of these diseases varies in different populations.

In fact, although the link between MGUS and multiple myeloma has been known for some time, it has never

(Photo: R. Baer)



Ola Landgren, M.D., Ph.D., and Mary Ann Yancey, R.N., examine a patient with multiple myeloma. Yancey is the lead research nurse for the Multiple Myeloma Section at CCR.

been established whether MGUS is a required stage in the development of multiple myeloma or just one of many paths to the disease. From the beautiful work of John Shaughnessy's laboratory at the University of Arkansas, we know, for example, that multiple myeloma is at least seven molecularly distinct disease subtypes and that some of these entities are relatively more indolent or aggressive. And we've done some preliminary work that indicates that, on average, African Americans have a better prognosis than Caucasians, which seems to be a reflection of the fact that they are more prone to the more indolent subtypes of multiple myeloma.

We were able to look at the relationship between MGUS and multiple myeloma longitudinally using an extraordinary NCI resource: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial that has charted the cancer histories of over 77,000 participants since its inception in 1992. These individuals, who were all cancer-free at the beginning of the trial, had blood work done every year for up to six years and have been followed for up to 10 years. From this trial, we identified 71 individuals who developed multiple myeloma over the course of the study and went back to the freezer to examine each of their blood samples.

In 100 percent of cases, we found MGUS abnormalities prior to the multiple myeloma diagnosis.

### Tracking the Transformation

Although a simple finding, this unyielding relationship between multiple myeloma and MGUS has enormous implications. Suddenly, we have a population that we can hone in on and state with confidence that all cases of multiple myeloma will arise from it. Another key finding in our PLCO-based study is the fact that about 50 percent of the MGUS patients had a steady increase in M-protein levels prior to the development of multiple myeloma, while the other 50 percent had a stable M protein and yet they developed myeloma. Thus, a stable M-protein level over time is not a reliable marker to rule out multiple myeloma progression. There is no doubt we need better markers.

We are taking several parallel approaches to address the need for better predictors of progression. For example, using stored blood samples of patients with MGUS and multiple myeloma, we are screening for biomarkers that signal progression. Also, newer imaging methods may give us insights into the course of the disease. We are currently developing a protocol that will take advantage of contrast agents to enhance imaging by positron emission tomography/computed tomography (PET/CT) and magnetic resonance (MR). Using these techniques, we will study patients with MGUS and newly diagnosed multiple myeloma in order to establish better clinical markers of progression. In this study, we will correlate our imaging results with traditional skeletal surveys and with several molecular biomarkers.

We have also just opened the first natural history study of myeloma precursor disease here at the NIH Clinical Center and we are actively seeking patients for this important study. We are enrolling people with MGUS and smoldering multiple myeloma (SMM) and following them for up to five years. SMM is a high-risk precursor disease defined based on higher levels of M protein ( $>3$  g/dL) or higher levels of plasma cells in the bone marrow (10 percent or more), or a combination. We will collect blood, bone marrow, and urine samples at multiple time points. The aim is to define molecular signatures for progressors versus non-progressors. At the moment, we don't have any molecular markers that definitively distinguish between MGUS, SMM and multiple myeloma—

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the diagnoses are based on clinical criteria.

Of course, we want to be able to identify the patients with MGUS that will go on to develop multiple myeloma. If you are diagnosed at the age of 40 and you live to the age of 90, that's 50 years of living with a one percent risk of transformation per year. For such an individual, the lifetime risk of developing multiple myeloma is 50 percent—essentially the same as flipping a coin. We need to identify the molecular signals that will allow us to predict individual risk scores with much greater accuracy.

But we want to do much more than just discover markers of these diseases. Our natural history study has the potential to provide novel biomarkers for the clinic and, at the same time, to uncover biological mechanisms of transformation. Ultimately, it will allow us to define new targets for early treatment of high-risk MGUS/SMM cases.

### No Cell Is an Island

There are a lot of molecular candidates that we can follow in our patient studies. And they don't just come from

studies of the plasma cells themselves. Disease progression in multiple myeloma is related to both intrinsic changes of plasma cells and the influence of the microenvironment—the bone marrow stromal cells, angiogenesis, and immunologic factors. MGUS and multiple myeloma cells appear to produce an abnormally broad superfamily of immunoreceptors that, when signaled by multiple factors, support sustained proliferation.

In our natural history study, we will be screening a broad range of markers. For example, we will look at gene expression profiles as well as cytokines and chemokines, either secreted by tumor cells or the environment, that have been reported as being important for myeloma progression. We are also looking at circulating proteasomes (molecular complexes that degrade proteins inside cells and that are often overproduced in cancer cells) and factors that are secreted in the bone marrow that are known to promote tumor proliferation. But there will surely be more possibilities as the mechanisms of pathogenesis are better understood.

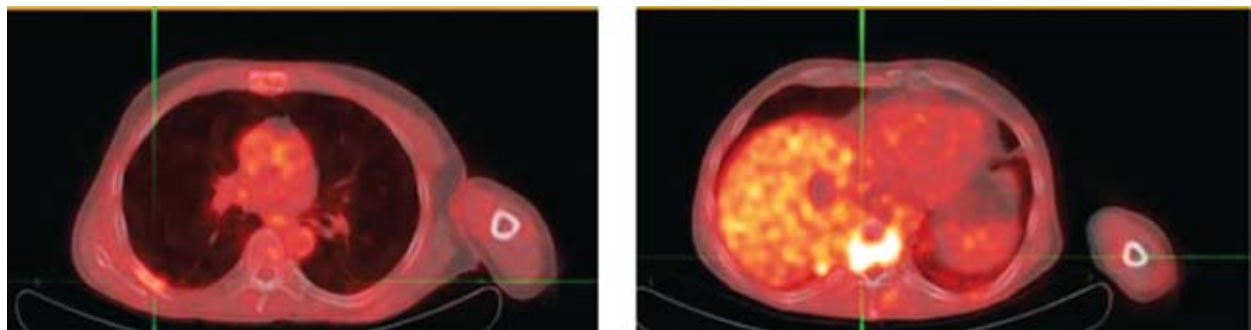
In a collaborative project including Michael Kuehl, M.D., Head of CCR's Molecular Pathogenesis of Myeloma Section, Pamela Gehron Robey, Ph.D., and Arun Balakumaran, M.D., Ph.D., at the National Institute of Dental and Craniofacial Research, and Adriana Zingone, M.D., Ph.D., at CCR's Multiple Myeloma Section, we are working on a mouse model of multiple myeloma. Dr. Robey developed a xenograft method

to induce human bone marrow stromal cells to produce small bone formations (ossicles) under the skin of these mice. We have been able to inject human myeloma cells into the ossicles. We are still working to further develop and validate this model, but our aim is to jump between our discovery work using human samples from biobanks, our prospective trials, and our mouse studies. For example, the mouse models may reveal disease mechanisms with signatures that we can look for in human samples. And in a complementary way, our human studies may suggest drug targets that we can test in our mouse models. The mouse model has potential to help us develop novel drugs and gain a better understanding of myeloma pathogenesis.

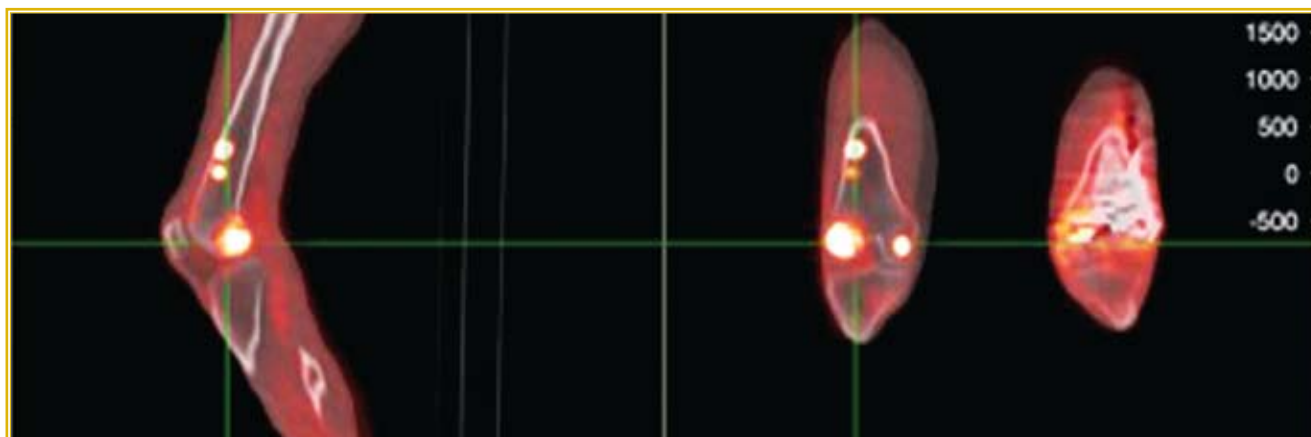
### Caught Is not Cured

Currently, patients diagnosed with multiple myeloma below the ages of 65-70, and without major comorbidities, are typically given a immunomodulatory agent (thalidomide or revlemid) and/or a proteasome inhibitor (bortezomib), in combination with steroids (dexamethasone). After courses with these drugs, stem cells are typically harvested and returned (autologous transplant) to the patient after treatment with high-dose melphalan. There is currently some debate and ongoing research on the need for autologous transplant/high-dose melphalan treatment as a consolidation in all patients. For patients above the ages of 65-70, who cannot

(Image: O. Landgren)



Bone lytic lesions in a patient with multiple myeloma, visualized with PET/CT imaging.



(Image: O. Landgren)

Bone lesions in the right distal femur of a patient with multiple myeloma, identified with 18F-FDG-PET/CT imaging.

tolerate autologous transplant/high-dose melphalan treatment, there are currently two FDA-approved treatment approaches. They are melphalan and the steroid prednisone in combination with either thalidomide or bortezomib.

None of the approved myeloma drugs are without toxic side effects and in my opinion, therefore, it is far too early to start treating patients with MGUS with currently available therapies. However, for SMM patients, the average risk of transformation reaches 50 percent within only five years; for SMM patients with certain adverse clinical features, the risk is 70-80 percent at five years of follow-up. The current standard of care for SMM patients is basically an aggressive “watch and wait” strategy until multiple myeloma is diagnosed. Based on small numbers, prior research has not supported early intervention with standard multiple myeloma chemotherapy regimens and there are theoretical reasons to be concerned that such intervention might paradoxically encourage the development of more aggressive myeloma clones.

Using novel approaches that are not based on conventional multiple myeloma therapy, we are currently developing a protocol to treat patients with SMM and hopefully delay or prevent progression to multiple myeloma. For example, in collaboration with Richard Childs, M.D., Ph.D., at the National Heart, Lung and Blood Institute, we are

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building on evidence that suggests that the innate immune system—and in particular, natural killer (NK) cells—may be fighting multiple myeloma. For this particular trial, we will be trying to encourage the activity of NK cells with a biologic, but we are also exploring other targeted strategies that include both immune-based and small-molecule approaches.

At the other end of the treatment spectrum, we are working on novel molecularly targeted therapies based on what we know about the signaling abnormalities that develop in refractory and/or relapsed multiple myeloma patients. For example, the MEK/ERK pathway is important in several tumor types, including multiple myeloma. Christina Annunziata, M.D., Ph.D., and Louis Staudt, M.D., Ph.D., in CCR’s Medical Oncology and Metabolism Branches, have screened myeloma cell lines and found genetic alterations that lead to activation of the MEK/ERK pathway. Furthermore, it turns out that the osteoclasts—cells that secrete growth factors into the microenvironment in which myeloma cells proliferate—are

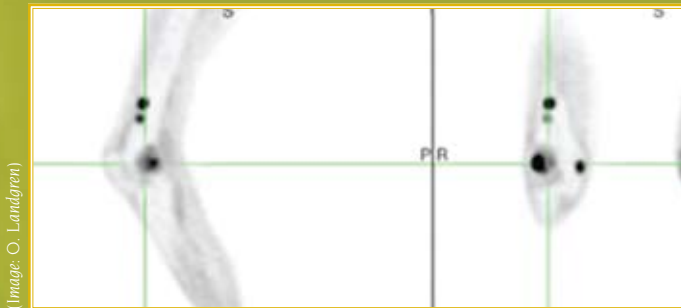
also impacted by inhibition of MEK in a way that might decrease myeloma proliferation and survival. This and other evidence has led us to a Phase 2 clinical trial in collaboration with the South East Phase II consortium led by Steven Grant, M.D., for the treatment of refractory multiple myeloma with an oral drug that inhibits MEK signaling.

It is really a very exciting time for our work. A lot of the research that we have built up over the years seems to be coming to fruition and we see multiple lines of investigation coming together to help define and treat multiple myeloma at all stages. Of course, there is still so much that we don’t know. When my 11-year-old daughter heard me talking about MGUS recently, she asked me, “What comes before the precursor?” And that’s a very good question. The answer is probably another precursor.

To learn more about Dr. Landgren’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?profileid=14864>.



# The Doctor-Patient Relationship



(Image: O. Landgren)

*A physician chanced upon his own diagnosis of MGUS, and now must wonder whether he will develop multiple myeloma.*

Jim M. practices internal medicine in the Washington, DC area. One day, he was running lab tests on his own blood—the reasons aren't important—and found that the total protein levels were highly elevated. Concerned, he began to run a series of tests to isolate the source of the excessive proteins. Using serum protein electrophoresis, he discovered higher-than-normal levels of M protein. In fact, as it turned out, the initial lab tests he had done on his total protein levels were erroneous and they were not elevated over the normal range. But the finding of excess M protein (a small percentage of total protein)—and with it, the diagnosis of MGUS—remained.

"It was a sheer random event," explained Jim. "There must be thousands of people walking around with MGUS and unaware of it." Jim knows that at his age—64 years—approximately three percent of the population has MGUS and that a small fraction of those will progress to multiple myeloma. "It's a terrible disease, but it is rare."

MGUS has no symptoms and no treatment. It is typically diagnosed when blood tests are done for other

reasons. "We've got tons of patients—several hundreds in our hospital facilities alone—that have MGUS," noted Jim. "The only thing to do is watch and watch and watch."

"Having a diagnosis of MGUS is a nuisance, a pain in the neck," said Jim. "It's a predisposition—no different from the people walking around with skin moles that may suddenly become a severe form of melanoma." Vigilance—in this case, frequent testing—is the only available tactic and there is currently no way of knowing whether the disease is transforming into outright cancer or any way to prevent that transformation from happening.

After his diagnosis, Jim happened to be talking with a hematologist colleague who had recently returned from the 2009 Annual Meeting of the American Society of Hematology. The colleague had heard that Dr. Ola Landgren was studying MGUS, enrolling individuals with MGUS in a prospective trial to uncover markers and mechanisms of transformation.

"The number of people in hematology that are actually doing research on this subject is miniscule because they are focusing on how

to cure multiple myeloma, not how you prevent something with a low likelihood of transformation," explained Jim. That's why he is enthusiastic about the work Dr. Landgren is undertaking. "I am most interested in the possibility of understanding why these cells change and begin to produce abnormal proteins."

"Ultimately, the question is, can you go in there and stop it," concluded Jim, noting that there aren't too many diseases where you can pick out precursors and could therefore intervene early. "Ideally, you would take some medicine and the next time you came in, there would be no abnormal proteins and a bone marrow biopsy would show no abnormal cells. We may be very far from that, but at least we are asking the questions."

*CCR's Understanding Targeted Therapies for Multiple Myeloma, an animated tutorial that explains some of the new approaches to treating this cancer, can be viewed at <http://www.cancer.gov/flash/targetedtherapies/multiplemyeloma/main.html#>.*